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Der Pharmacia Lettre, 2016, 8 (19):269-274
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ISSN 0975-5071
USA CODEN: DPLEB4

Toxic nephropathy due to bromobenzene intoxication and the protective role of alternative medicines

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ABSTRACT

Bromobenzene is an environmental toxin. Exposure to bromobenzene causes injury to hepatic and extra-hepatic tissues. The secondary metabolites of bromobenzene are toxic to kidneys. Bromobenzene is capable of causing ATP depletion, mitochondrial dysfunction, local inflammation, lipid peroxidation and subsequent loss of cellular function and integrity. This review provides insights into the mechanisms involved in bromobenzene intoxication and the effectiveness of several alternative medicines studied so far against bromobenzene-induced nephrotoxicity.

Keywords: Bromobenzene, hepatotoxicity, oxidative damage, alternative medicines

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INTRODUCTION

Drug-induced nephrotoxicity is seen as a common cause of many therapeutic drugs. Cases of acute renal injury have been increasingly reported since last two decades and are found to be the cause of morbidity and mortality [1]. Drugs such as aminoglycoside antibiotics, amphotericin B, non-steroidal anti-inflammatory drugs (NSAIDS), certain cyclo-oxygenase-2 (COX-2) inhibitors and angiotensin-converting enzyme inhibitors (ACEIs) have been frequently reported to cause drug-induced nephrotoxicity [2]. Drugs like rifampicin, isoniazid, anti-malarials, anti-virals, penicillin, cephalosporins, sulfonamides, aminosalicylic acid and methyldopa are capable of causing hemolysis and myoglobinuria possibly leading to renal failure [3,4]. Some of the common patient-related risk factors for drug-induced nephrotoxicity are age above 60 years, renal insufficiency, diabetes, heart failure and sepsis [5].

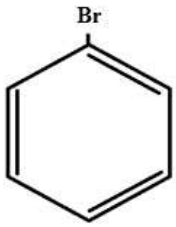
Apart from these therapeutic agents there are also several environmental pollutants and industrial chemicals that may lead to the development of acute and chronic kidney disease [6]. Heavy metals like cadmium, lead, chromium, uranium and mercury are also nephrotoxic. They cause toxicity in kidneys by reducing the renal blood flow thereby affection the glomerular filtration [7]. Another mechanism that has been found in metal-induced nephrotoxicity is glutathione (GSH) conjugation and in addition binding of these metals to metallothionein is also a significant process [8]. Both these mechanisms lead to bioaccumulation of these metals rather than serving as defense mechanisms. Chemicals which are halogenated hydrocarbons like trichloroethane and chloroform conjugate with GSH in the liver before they are taken up by the kidneys causing nephrotoxicity [9,10]. In particular, the anatomical features and physiological functions of the kidney make it the target organ for these toxicants upon their conjugation with GSH. This initiates different mechanisms resulting in the inhibition of renal function. Furthermore, the compounds that are not water soluble precipitate in the tubules causing obstruction in the tubular flow and subsequently cause damage to the architecture of the tubular epithelium. There may be cell death contributed by both apoptosis and necrosis in acute renal injury [11].

PHYSICO-CHEMICAL PROPERTIES OF BB

Human beings are exposed to a variety of chemicals and pollutants on daily basis that result in serious health defects. Bromobenzene (BB) is a xenobiotic which is released into the environment during its production in industries. This halogenated hydrocarbon (Figure 1) has a molecular mass of 157.01 g/mol and is a colorless liquid

with a pungent odor [12]. It is widely used as an additive in motor oil and as a solvent for large scale crystallizations. The harmful chemical is also used to produce phenyl magnesium bromide. Table 1 shows certain physical and chemical properties of BB.

Figure 1: Structure of bromobenzene



BIOTRANSFORMATION OF BB

The biotransformation of BB is regulated by the members of the nuclear receptor superfamily like any other xenobiotic. This includes the steroid receptors such as the estrogen and the androgen receptors and the non-steroid receptors such as the Pregnane X Receptor (PXR), Constitutive Androstane Receptor (CAR), Peroxisome Proliferator-Activated Receptors (PPAR) and the Aryl Hydrocarbon Receptor (AHR). These receptors act as xenobiotic sensors that are involved in the transcriptional regulation of the enzymes involved in the metabolism of the xenobiotics. The metabolism of xenobiotics occurs in three phases of which the phase I detoxification involves the monooxygenation process which is catalyzed by the cytochrome P450 (CYP450) enzymes while the phase II biotransformation involves mainly the conjugation process where glucoronidation, acetylation, sulfation, methylation and GSH and amino acid conjugation take place [13]. Phase III involves the ATP-Binding Cassette (ABC) family of receptors which are active membrane transporters involved in the transportation of xenobiotics across cellular membranes [14].

Table 1: Physical and chemical properties of BB

Boiling point	156.0ºC (Lide, 2000)
Melting point	-30.6ºC (Lide, 2000)
Density	1.4950 g/ml at 20ºC (Lide, 2000)
Viscosity	1.124 cp at 20ºC (Budavari, 2001)
Vapour pressure	4.18 mm Hg at 25ºC (Riddick *et al*., 1986)
Vapour density	2.46 (air = 1) (Budavari, 2001)
Water solubility	4.46 x 10^2 mg/L at 30ºC (Chiou *et al*., 1977)
Partition coefficient	log K_{ow} = 2.99 (Hansch *et al*., 1995)
Critical temperature	397ºC (Budavari, 2001)
Critical pressure	33, 912 mm Hg (Budavari, 2001)

The CAR induces the transcriptional activation of certain CYP genes (CYP2B, CYP2C, CYP3A), NADPH-CYP reductase, Glutathione-S-Tranferase (GST), sulfotranferases (STs) and UDP-glucuronosyltransferases (UGTs) [15]. CAR also plays an important role in the upregulation of genes that encode the xenobiotic transporters Mrp2 and Mrp4 [16]. PXR is another key regulator of xenobiotic metabolism and functions along with CAR in regulating the expression of the CYP genes and its distribution in the tissues resembles that of CAR [17]. Recently, these two orphan nuclear receptors are looked up on as potential targets for treating metabolic disorders as they also possess endobiotic functions that have effects on the pathogenesis of such disorders [18]. The discovery of these two potent regulators of xenobiotic metabolism has led to extensive research at gene level in xenobiotic toxicology.

ANTIOXIDANT DEPLETION DUE TO BB INTOXICATION

Ingestion of food contaminated with BB or exposure by dermal contact or ingestion in cases of occupational exposure is followed by the metabolism of BB in liver leading to hepatotoxicity (Figure 2). BB is capable of causing ATP depletion, mitochondrial dysfunction, local inflammation, lipid peroxidation and subsequent loss of cellular function and integrity [19]. It induces liver necrosis in rats and mice [20,21] especially zonal necrosis in the hepatic acinus as seen in experimental rats [22]. BB is converted to 3, 4- bromobenzene oxide which binds covalently to the hepatic tissue macromolecules on biotransformation of BB in liver [21,23]. The reactive epoxides of BB conjugate with GSH, thus reducing the hepatic GSH and also impairing the protection against reactive oxygen species (ROS) [24,25]. There is a strong correlation between GSH depletion, lipid peroxidation and the development of liver necrosis [26].

Furthermore, the secondary metabolites of BB (*ortho*-bromophenol, 2-bromohydroquinone, alpha and beta unsaturated epoxides of BB) that are formed on biotransformation of BB in the liver and their glutathione conjugates are found to be highly toxic to the kidneys [27,28]. The reactive oxygen species (ROS) generated during the process mediate the nephrotoxic effect of BB leading to renal necrosis and tubular degeneration [29]. Studies in experimental rats have shown that agents with antioxidant property ameliorate the toxic effects of drug-induced hepatotoxicity and nephrotoxicity [30,31].

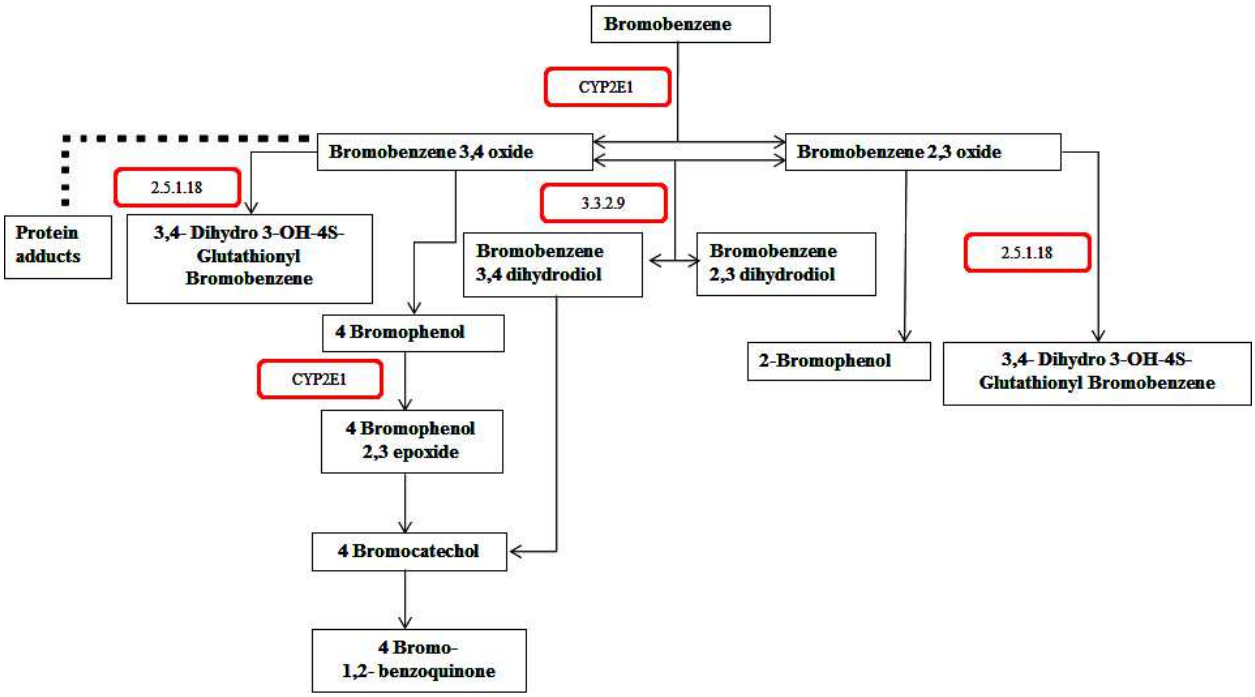


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Figure 2: Biotransformation of bromobenzene in the liver

NEPHROTOXIC EFFECT OF BB

The metabolites of BB formed in the liver conjugate with GSH causing nephrotoxicity. The nephrotoxic role of *ortho*-bromophenol following BB administration in rats has been studied and it was proved that *o*-bromophenol covalently binds four times greater to kidney protein than to liver protein [32]. Several studies show that such GSH conjugates elicit renal damage. The nephrotoxic role of 2-bromohydroquinone which is a metabolite of BB and *o*-bromophenol has been studied in experimental rats [33]. The administration of 4-bromocatechol in mice showed renal cortical necrosis in mice indicating its role as a potent nephrotoxicant in BB-induced nephrotoxicity [29]. The nephrotoxic role of GSH conjugates of 2- bromohydroquinone has been demonstrated by the intravenous injection of these GSH conjugates in rats followed by increase in blood urea nitrogen (BUN) levels [33]. The toxicity caused due to BB and its metabolites on rabbit proximal tubules was demonstrated *in vitro* and it is found that 2-bromohydroquinone was the major toxicant that contributed to BB-induced nephrotoxicity [34]. The renal covalent binding of 2-bromohydroquinone and the effect on γ- glutamyl transpeptidase activity were demonstrated in male Sprague-Dawley rats and this study also showed that there was a 70% increase in the BUN levels [35]. The administration of 2-bromophenol in rats showed increased urinary excretion of renal epithelial cells and proteins [28].

MECHANISMS OF RENAL INJURY AND CELL DEATH

The mechanisms of toxic renal injury and cell death include ATP depletion that disrupts the architecture of the proximal tubular epithelium leading to an imbalance in the Na^+ pump-leak mechanism and as a result there is swelling of the cells which is characteristic of necrosis [36] (Figure 4).

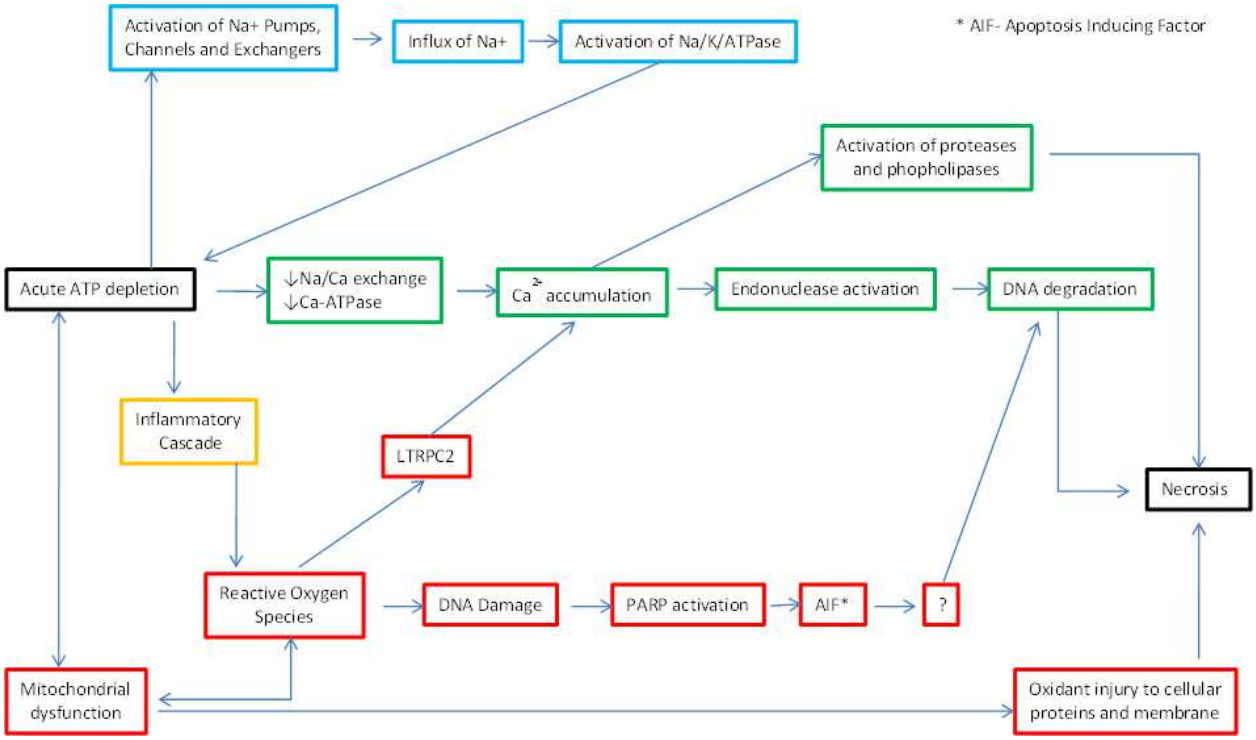

Figure 3: Hypothetical events leading to renal cell injury

Also there is increased cystolic Ca^{2+} levels that contributes to the activation of the Ca^{2+} dependent proteases like calpain (a member of the family of Ca^{2+} dependent, non-lysosomal cysteine proteases), endonucleases and phospholipases resulting in constitutive activation of the proximal tubules in response to toxic injuries. Furthermore, the generation of reactive oxygen species (ROS) in toxic renal injury causes increased lipid peroxidation, protein denaturation and DNA damage. Cyclooxygenases, lipoxygenases, xanthine oxidase and impaired mitochondrial electron transport chain are the main sources of ROS in acute renal injury [37]. TNF receptor mediated apoptosis also contributes fairly to acute renal injury and cell death in toxic conditions. Apoptosis is also induced by the generation of ROS, release cytochrome *c*, apoptotic factors and Bcl_2 family members by the mitochondria and alterations in the permeability transitions [11]. Studies have shown that treatment with antioxidants and free radical scavengers ameliorated renal injury.

ALTERNATIVE MEDICINES AGAINST BB INTOXICATION

Effect of herbal drugs in bb intoxication

Several studies have been carried out in order to establish the protective effects of various natural agents in BB-induced nephrotoxicity. The administration of crude alcoholic-extract of *Cassia fistula* fruit in BB-intoxicated mice showed to protect them from renal toxicity due to BB which was demonstrated by the assessment of BUN and creatinine levels and kidney histology [38]. The protective effect of the extract of *Phyllanthus fraternus* against BB-induced mitochondrial dysfunction in rat kidney was compared with that vitamin E and it was shown that the extract was able to restore normal antioxidant status and kidney histology in BB-induced nephrotoxicity [39]. The administration of *Spirulina fusiformis* in BB-intoxicated rats showed that the algae significantly attenuated the nephrotoxic effects of BB in Wistar albino rats [40].

Nigella sativa L. seed oil commonly known as black seed oil renders protection against BB-induced hepato-renal toxicity in rats. The administration of black seed oil was shown to normalize the kidney function indices and also prevented morphological changes in kidney architecture [41]. The traditional Indian herb *Hemidesmus indicus* L. R. Br. has also shown protective effects against BB-induced impairment of mitochondrial function in rat kidneys [39]. It is proven that this herb has free radical scavenging properties. The root powder of *Withania somnifera* L. alleviates mitochondrial oxidative stress in the kidneys of BB-induced rats [40]. The herb is well-known for its antioxidant potential and this could be the reason for its protective role against mitochondrial dysfunction in BB intoxication.

Effect of herbal formulations in bb intoxication

The Japanese herbal formulation 'Juzen-taiho-to' commonly known as Kampo has been proven to be effective in modulating oxidative stress in BB-induced rats [42]. The traditional Indian Ayurvedic formulation Triphala is also

protective against BB intoxication as the formulation contains components (*Terminalia bellirica* (Gaertn.) Roxb., *Terminalia chebula* Retz., *Emblica officinalis* Gaertn.) with potent antioxidant activity namely [43].

Protective compounds against bb intoxication

Withaferin A, an active compound of *Withania somnifera* possesses protective effect against BB-induced renal oxidative stress [44]. The phytocompound renders protection against BB-induced changes in serum markers of renal function, cytokines such as TNF-α and IL-1β and also normalize the alterations in Bcl-2/BAX ratio. The flavonoid hispidulin was found to prevent glutathione depletion in BB-induced mice thereby indicating its potential antioxidant activity [45]. The administration of cysteine prodrugs was capable of enhancing the clearance of the metabolites of BB in urine [46].

CONCLUSION

Renal dysfunction and injury occur as a result of interaction between some of the free radicals and various tissue components. The formation of reactive metabolites and oxidative stress result in the damage of kidneys in BB-treated rats. Increased lipid peroxidation leads to loss of cell membrane integrity and initiates membrane bound enzyme activity which damages the cell structure and function. This review provides insights into the mechanisms of BB-induced renal toxicity and effective alternative therapies for the same.

Acknowledgement

The authors are thankful to VIT University for providing the facilities to carry out the research work.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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